Evolutionary Games with Affine Fitness Functions: Applications to Cancer

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Abstract We analyze the dynamics of evolutionary games in which fitness is defined as an affine function of the expected payoff and a constant contribution. The resulting inhomogeneous replicator equation has an homogeneous equivalent with modified payoffs. The affine terms also influence the stochastic dynamics of a two-strategy Moran model of a finite population. We then apply the affine fitness function in a model for tumor-normal cell interactions to determine which are the most successful tumor strategies. In order to analyze the dynamics of concurrent strategies within a tumor population, we extend the model to a three-strategy game involving distinct tumor cell types as well as normal cells. In this model, interaction with normal cells, in combination with an increased constant fitness, is the most effective way of establishing a population of tumor cells in normal tissue.

Keywords Evolutionary Game Theory · Replicator Equation · Cancer · Stroma · Prisoner's Dilemma · Moran Process

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1 Introduction

Evolutionary dynamics describes changes in populations of competing individuals over time (Nowak, 2006a). These changes depend on the notion of fitness, a quantity that describes how many offspring a member of the population is expected to produce. In the simplest model of fitness, the number of offspring depends only on the individual itself and not on other individuals or the environment. More generally, fitness may be modeled as frequency-dependent, accounting for interactions among individuals. In evolutionary game theory, fitness is modeled as the outcome of a game whose players adopt distinct strategies; in this framework, individuals are identified with the strategy they play (Maynard Smith, 1982; Hofbauer and Sigmund, 2003). The fitness assigned to a given strategy is typically defined as the expected payoff resulting from playing the game with all other strategies present in the population, and in this case, fitness is a linear function of the frequencies. Recently, nonlinear fitness functions have also been discussed (Taylor and Nowak, 2006; Prügel-Bennett, 1994; Altrock and Traulsen, 2009; Traulsen et al., 2008, 2007).

An example of an evolving system is the cell population of a tumor. Tumors arise from normal cells in an organism through mutations that increase their somatic fitness, which leads to outgrowth of normal tissue by the tumor and eventually to invasion of other organs (Cairns, 1975; Nowell, 1976). The increased proliferation of cancer cells is, in part, due to interactions with normal cells (Axelrod et al., 2006). One example of tumor-stroma interactions is vascular endothelial growth factor (VEGF) signaling (Mueller and Fusenig, 2004). Many tumors secrete the mobile growth factor VEGF which stimulates the production of blood vessels. Angiogenesis, in turn, increases the fitness of tumor cells through the supply with nutrients and oxygen. Using experimental and bioinformatics methods, it has recently been estimated that cancer cells make up only 49% of the cells in tumor tissue (Van Loo et al., 2010). The surprisingly high fraction of normal cells in a tumor indicates that normal cells play an important role in tumor development. However, it remains elusive to which extent the interaction between normal and tumor cells may contribute to the proliferative advantage of tumor cells.

To quantify the somatic evolution of tumors mathematical models are used (Michor et al., 2004). Approaches include population genetics models (Beerenwinkel et al., 2007; Durrett et al., 2009; Gerstung and Beerenwinkel, 2010; Bozic et al., 2010) that describe the accumulation of driver mutations which confer a fitness advantage to the tumor cells, and evolutionary game theory models (Basanta and Deutsch, 2008). Game-theoretic approaches were used to describe both interactions of tumor cells with the environment (Gatenby and Vincent, 2003) as well as among tumor cells (Tomlinson, 1997). Interactions are not restricted to be pairwise. For example, Dingli et al. (2009) recently analyzed the joint interactions of multiple myeloma cells with osteoclast and osteoblast cells in the framework of evolutionary games.

In the present work, we model fitness to be composed both of a game-theoretic interaction term and a constant term specific to each cell type. This

choice is motivated by the fact that cancer cells harbor multiple mutations, which can affect cell-cell interactions, alter intrinsic behavior, or both. Hence, the fitness function is an affine function of the relative frequencies of normal and tumor cells.

We first analyze the evolutionary dynamics in general in the framework of the replicator equation. Specifically, we clarify the role of the interaction term relative to the constant fitness term. We show that the Prisoner's Dilemma game, which does not allow for the evolution of cooperation, is transformed by adding a constant fitness term in such a way that cooperation becomes possible for certain parameter choices of the affine fitness function. We also analyze how the affine fitness terms affect the stability criteria for a Moran model of a two-strategy game in a finite population.

The results for the continuous replicator model are then applied to assess whether exploitation of normal cells or intrinsic proliferation is more evolutionarily favorable for a tumor cell. We analyze a set of tumor strategies leading to the same equilibrium with normal cells in a pairwise game, and find that the strategy with both a constant fitness advantage and attraction of normal cells is most successful in the competition with other tumor strategies.

2 Inhomogeneous evolutionary games in infinite populations

We consider a game with n strategies and payoff matrix $\boldsymbol{M} \in \mathbb{R}^{n \times n}$. The entry m_{ij} of $\boldsymbol{M}$ denotes the payoff to strategy i if playing against strategy j. In evolutionary game theory, a fixed strategy is associated to each individual. In our application, we think of the strategy as being determined by the genetic changes of the cancer cell and we identify strategies with genotypes and with cell types. We first assume an infinite population size and describe the state of the population by the vector

$$\mathbf{x} \in S_{n-1} = \left\{ \mathbf{x} \in [0,1]^n \;\Big|\; \sum_{i=1}^{n} x_i = 1 \right\} \tag{1}$$

of relative strategy frequencies. The state space S_{n-1} is the $(n-1)$-dimensional probability simplex. The fitness of a type i individual is the expected payoff

$$f_i(\mathbf{x}) = \sum_{j=1}^{n} m_{ij} x_j. \tag{2}$$

Let us assume now that fitness is composed of such a linear term arising from a game plus a constant term $r_i \in \mathbb{R}$. In vector notation, the resulting affine fitness function is

$$f(\mathbf{x}) = \boldsymbol{M}\mathbf{x} + \mathbf{r} \tag{3}$$

where $\mathbf{r} \in \mathbb{R}^n$. For $\mathbf{r} = (0, \ldots, 0)^\top$, we recover the strong selection limit, where fitness is directly given by the expected payoff of the game. For $w \in \mathbb{R}_+$, $w \ll 1$, and $\mathbf{r} = (1 - w, \ldots, 1 - w)^\top$, the affine fitness function can be interpreted as

that of the game with payoff $\boldsymbol{M}' := (1/w)\boldsymbol{M}$ in the weak selection limit: $f(\mathbf{x}) = w\boldsymbol{M}'\mathbf{x} + (1-w,\ldots,1-w)^\top$. In both limiting cases, all components of the constant term $\mathbf{r}$ are identical. In the following, we relax this constraint and allow the components r_i to be different for each strategy.

For infinite population size, the dynamics of reproducing individuals can be described by the replicator equation (Taylor and Jonker, 1978; Zeeman, 1980; Schuster and Sigmund, 1983) as

$$\dot{x}_i = x_i\left[f_i(\mathbf{x}) - \phi(\mathbf{x})\right], \quad i = 1,\ldots,n \tag{4}$$

where $\phi(\mathbf{x}) = \mathbf{x}^\top f(\mathbf{x})$ is the average fitness of the population. The fixed points of this system are the solutions of the set of algebraic equations $\dot{\mathbf{x}} = 0$. The replicator equation always has the n trivial solutions $\mathbf{x}^*$ given by $x_i^* = 1$ and $x_j^* = 0$, for all $j \neq i$. Hofbauer and Sigmund (1998) provide a general proof for the possible number of internal equilibria in two-player, n-strategy games. A more general system is considered in Gokhale and Traulsen (2010).

For the affine fitness function defined in Eq. 3, the replicator equation 4 is said to be inhomogeneous. The inhomogeneous replicator equation can be interpreted as the (homogeneous) replicator equation of a transformed game.

Theorem 1 (Stadler, 1991) *The inhomogeneous replicator equation with affine fitness function $f(\mathbf{x}) = \boldsymbol{M}\mathbf{x} + \mathbf{r}$ is equivalent to the homogeneous replicator equation with linear fitness function $f'(\mathbf{x}) = \boldsymbol{M}'\mathbf{x}$ with*

$$m'_{ij} = m_{ij} + r_i. \tag{5}$$

Proof Because $\sum_{j=1}^n x_j = 1$, one has

$$f'_i(\mathbf{x}) = \sum_{j=1}^n (m_{ij} + r_i)x_j = \sum_{j=1}^n m_{ij}x_j + r_i = f_i(\mathbf{x}). \tag{6}$$

It follows that $\phi'(\mathbf{x}) = \mathbf{x}^\top f'(\mathbf{x}) = \phi(\mathbf{x})$. Hence we have $f_i(\mathbf{x}) - \phi(\mathbf{x}) = f'_i(\mathbf{x}) - \phi'(\mathbf{x})$, which completes the proof.

Theorem 1 shows that the replicator dynamics induced by an affine fitness function can be obtained from an equivalent homogeneous replicator equation. However the evolutionary dynamics of the transformed game $\boldsymbol{M}'$ can be substantially different from the one based on $\boldsymbol{M}$ alone.

3 Two-player games in infinite populations

Passing from a linear to an affine fitness function by adding a constant fitness term shifts the equilibrium of the replicator equation. We consider the inhomogeneous replicator equation for two types of individuals (strategies) A and B with

$$\boldsymbol{M} = \begin{matrix} & A & B \\ A & \\ B & \end{matrix}\begin{pmatrix} a & b \\ c & d \end{pmatrix} \qquad \text{and} \qquad \mathbf{r} = \begin{pmatrix} s \\ t \end{pmatrix}. \tag{7}$$

Behavior	Schematic	Parameter Range
Stable internal equilibrium	$A \rightarrow x^* \leftarrow B$	$\alpha < \sigma < \beta$
Unstable internal equilibrium	$A \leftarrow x^* \rightarrow B$	$\alpha > \sigma > \beta$
A dominates B	$A \longleftarrow B$	$\sigma < \alpha, \beta$
B dominates A	$A \longrightarrow B$	$\sigma > \alpha, \beta$

Table 1 Stability of the 2-strategy replicator equation with affine fitness function with game M and offset $\mathbf{r}$, Eq. 7. Parameters are as in Eq. 8. Arrows indicate the change in the composition of the population over time.

By Theorem 1, there exists a non-trivial fixed point in which the proportion of A individuals in the population is given by

$$x^* = \frac{\beta - \sigma}{\beta - \alpha}, \tag{8}$$

where we have defined $\alpha = a - c$, $\beta = b - d$, and $\sigma = t - s$. The fixed point x^* is attractive and in $(0, 1)$ if and only if

$$\alpha < \sigma < \beta, \tag{9}$$

that is, if the difference in constant fitness σ is between the differences in payoff α and β. It follows that for any game with $\alpha < \beta$ there exist constant fitness contributions r such that σ satisfies (9) and x^* is a stable, non-trivial equilibrium point.

Apart from the stable equilibrium, dominance of A (denoted by $B \rightarrow A$), dominance of B ($A \rightarrow B$), and an unstable equilibrium at x^* are possible. The parameter regimes leading to these dynamics are summarized in Table 1.

3.1 The Prisoner's Dilemma

The Prisoner's Dilemma is a metaphor for the evolution of cooperation (Axelrod and Hamilton, 1981). This game is defined by the inequalities

$$b < d < a < c \tag{10}$$

Strategy A is called cooperation and denoted C, whereas strategy B is called defection and denoted D. The inequalities imply that $\alpha, \beta < 0$. For linear fitness functions, the non-trivial fixed point x^* lies outside of the unit interval; thus $x_A = 0$, $x_B = 1$ is the only attractive fixed point and cooperation cannot evolve in this model.

For affine fitness functions, however, there does exist a stable equilibrium between cooperators and defectors provided that $\alpha < \sigma < \beta$, as shown in the previous section (Figure 1). The necessary condition $\alpha < \beta$ does not hold for all Prisoner's Dilemma games. If $\beta < \alpha$, then there exists only an unstable fixed point in $(0, 1)$ (Figure 1). In both cases, the all-cooperator equilibrium is stable, since $\sigma < \beta$. It is unique if in addition $\sigma < \min\{\alpha, \beta\}$. In this regime, constant selection dominates the dynamics of the evolutionary game, always
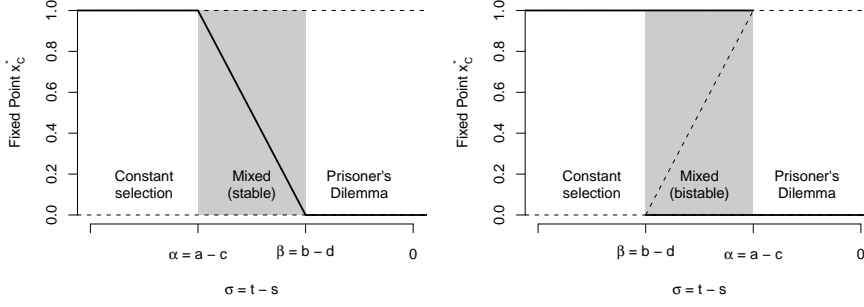
Fig. 1 Prisoner's Dilemma game with constant fitness advantage σ of the cooperators. The solid black lines denote the frequency of cooperators x_C^* at the stable fixed point $x^* = (x_C^*, x_D^*)^\top$ as a function of $\sigma = t - s$. Dashed lines are unstable fixed points. For $\alpha < \beta$, there exists a stable equilibrium (left, grey area) if $\alpha < \sigma < \beta$. For $\beta < \alpha$, the internal fixed point at $\beta < \sigma < \alpha$ is unstable (right plot). For the homogeneous Prisoner's Dilemma, $\sigma = 0$, defection is always stable.

favouring cooperators over defectors. Conversely, if $\sigma > \alpha$, there exists a stable all-defectors equilibrium, which is unique if in addition $\sigma > \max\{\alpha, \beta\}$.

The Prisoner's Dilemma has been studied in many variations in order to derive conditions under which cooperation can evolve. For example, Nowak (2006a) listed five rules for the evolution of cooperation. To formulate and to compare these rules, often a simplified version of the Prisoner's Dilemma is considered, where a cost $\mathfrak{c}$ is paid for cooperation, of which other cells receive a benefit $\mathfrak{b}$. Defectors do not pay a cost, and other cells do not receive a benefit from defectors:

$$
\boldsymbol{M} = \begin{matrix} \\ C \\ D \end{matrix} \begin{pmatrix} \overset{C}{\mathfrak{b} - \mathfrak{c}} & \overset{D}{-\mathfrak{c}} \\ \mathfrak{b} & 0 \end{pmatrix} \tag{11}
$$

We consider the affine fitness function obtained from this simplified Prisoner's Dilemma game plus a constant fitness term. Because $\alpha = \beta = -\mathfrak{c}$, the replicator dynamics do not allow for stable coexistence between cooperators and defectors. However, both pure strategies can be stable, namely cooperation for $\sigma < -\mathfrak{c}$, or equivalently,

$$
t - s > \mathfrak{c} \tag{12}
$$

and defection otherwise (Figure 1). Hence, selection favors cooperators if the constant fitness advantage is higher than the cost to pay for cooperation. This rule for the evolution of cooperation makes precise the tradeoff between constant fitness contributions and those resulting from playing the Prisoner's Dilemma game.

4 Inhomogeneous two-player games in finite populations

The deterministic replicator equation describes the dynamics of infinite populations. In finite populations a stochastic description in which interactions between members of the population are considered individually is more appropriate.

We consider a finite population of constant size N, containing as before two types of individuals (strategies) A and B. $\boldsymbol{M}$ and $\mathbf{r}$ are defined as in Eq. 7. Let i denote the number of A individuals in the population, and denote by F_i and G_i the sum of the expected game payoff and the constant fitness term for types A and B respectively. We have

$$F_i = \frac{(i-1)a + (N-i)b}{N-1} + s = \frac{(i-1)(a+s) + (N-i)(b+s)}{N-1} \tag{13}$$

$$G_i = \frac{ic + (N-i-1)d}{N-1} + t = \frac{i(c+t) + (N-i-1)(d+t)}{N-1}. \tag{14}$$

Also for a finite population the entries of $\boldsymbol{M}$ may be transformed according to Eq. 5 to an equivalent homogeneous game $\boldsymbol{M}'$. Yet the resulting changes of the stochastic dynamics in a finite population differ from those that arise in an infinite population. In the following, we discuss three different measures for the evolutionary success of a strategy in a finite population and study how these are affected by the constant fitness terms.

Following Nowak et al. (2004), we say that A resists invasion by B, or that A is an evolutionarily stable strategy (ESS$_N$), if $G_{N-1} < F_{N-1}$, i.e., if one B individual in an otherwise all-A population has lower fitness than the B individuals. This condition may equivalently be written as

$$(N-1)(\alpha - \sigma) > a - b, \tag{15}$$

where $\sigma = t - s$, as above. Note that for $N \to \infty$, this condition is equivalent to $\sigma < \alpha$, from which it follows that $x_A = 0$ is an unstable fixed point of the replicator equation (Table 1). Similarly, one obtains that B is ESS$_N$ if $F_{N-1} > G_{N-1}$, or

$$(N-1)(\beta - \sigma) < c - d, \tag{16}$$

which is for large N again equivalent to $\sigma < \beta$.

The Moran process (Moran, 1962) provides one model for evolutionary dynamics in finite populations. In each step of the process, one individual is chosen to reproduce with probability proportional to its fitness; its offspring replaces another individual, chosen at random from the population. Denote by $P_{i,j}$ the probability that given i A individuals, one step of the process yields j A individuals. We have

$$P_{i,i+1} = \frac{if_i}{if_i + (N-i)g_i} \cdot \frac{N-i}{N} \tag{17}$$

$$P_{i,i-1} = \frac{(N-i)g_i}{if_i + (N-i)g_i} \cdot \frac{i}{N} \tag{18}$$

$$P_{i,i} = 1 - P_{i,i+1} - P_{i,i-1}, \tag{19}$$

and $P_{i,j} = 0$ otherwise. To compute the fixation probabilities in the presence of an affine fitness term, we consider the limit of weak selection (Taylor et al., 2004; Antal and Scheuring, 2006; Lessard and Ladret, 2007; Wu et al., 2010). We define the frequency-dependent fitness for types A and B, respectively, by

$$f_i = 1 - w + wF_i \tag{20}$$

$$g_i = 1 - w + wG_i, \tag{21}$$

where the parameter $w \in (0,1)$ defines the intensity of selection. Small values of w indicate near-neutral evolutionary pressure (Kimura, 1985; Ohta, 2002)

The fixation probability of type A, i.e., the probability that one A individual will take over an otherwise all-B population, in the Moran process is $\rho_A = [1 + \sum_{k=1}^{N-1} \prod_{i=1}^{k} (g_i/f_i)]^{-1}$ (Karlin and Taylor, 1975; Taylor et al., 2004). For small w a power series expansion yields

$$\rho_A = \frac{1}{N} \cdot \frac{1}{1 - w\left((xN - y)/6 - (N-1)\sigma/2\right)}, \tag{22}$$

where $x = a + 2b - c - 2d = \alpha + 2\beta$ and $y = 2a + b + c - 4d$ (Nowak, 2006a). Further details about the convergence of the weak selection limit can be found in Wu et al. (2010).

For an A mutant with no fitness advantage over B, we have $\rho_A = 1/N$. We say A is advantageous (AD), if selection favors the fixation of A, $\rho_A > 1/N$, or equivalently

$$xN - y - 3(N-1)\sigma > 0. \tag{23}$$

For large N, this becomes

$$\sigma < \frac{\alpha + 2\beta}{3}. \tag{24}$$

Hence this condition is fulfilled if the condition $\sigma < \alpha, \beta$ for the replicator equation holds. Equilibrium is reached when $F_i = G_i$, or equivalently

$$i = \frac{\beta - \sigma}{\beta - \alpha}, \tag{25}$$

in agreement with the continuous case, Eq. 8.

Lastly, we say A is risk-dominant (RD) over B if $\rho_A > \rho_B$. In the case of weak selection, this is equivalent to

$$\frac{\alpha + \beta}{2}N - 6(a - d) - (N-1)\sigma > 0. \tag{26}$$

For large N, A is RD if, and only if

$$\frac{\alpha + \beta}{2} - \sigma > 0 \tag{27}$$

holds. The criteria for AD, ESS_N, and RD are summarized in Table 2. Note that all are fulfilled if $\sigma < \alpha$, as required for A to be evolutionarily stable in the replicator equation.

Criterion	Small population	Large population
ESS_N	$(N-1)(\alpha - \sigma) < a - b$	$\sigma < \alpha$
AD	$xN - y - 3(N-1)\sigma > 0$	$\sigma < (\alpha + 2\beta)/3$
RD	$(\alpha + \beta)N/2 - 6(a - d) - (N-1)\sigma > 0$	$\sigma < (\alpha + \beta)/2$

Table 2 Criteria for the evolutionary stability of strategy A in finite populations of small and large size.

As N grows large it is also possible to compute the expected time until fixation. As shown by Antal and Scheuring (2006), the fixation time for an AD strategy starting from a single mutant scales like $N \ln N$, whereas that of a neutral strategy scales like N^2. The affine modification affects whether a strategy is advantageous but not the scaling of the fixation time.

4.1 Affine Prisoner's Dilemma in finite populations

We return to the affine modification of the Prisoner's Dilemma defined in Eq. 11, considering it now in a finite population of size N. We have

$$\rho_C = \frac{1}{N} \cdot \frac{1}{1 + \frac{w}{2}((N-1)(\sigma + \mathfrak{c}) - \mathfrak{b})}. \tag{28}$$

Cooperation is AD, $\rho_C > 1/N$, if

$$-\sigma > \mathfrak{c} - \frac{\mathfrak{b}}{N-1}. \tag{29}$$

That is, the constant fitness advantage $-\sigma$ must be larger than the cost of cooperation $\mathfrak{c}$ minus the benefit $\mathfrak{b}$ divided by the population size minus one. It thus appears that the fixation probability of cooperators is higher in small populations, than in large ones. For $N \to \infty$ condition Eq. 29 results in $-\sigma > \mathfrak{c}$, again in agreement with the continuous case.

Because we have $\alpha = -\mathfrak{c} = \beta$, the conditions for ESS_N and RD are equivalent to $-\sigma > \mathfrak{c}$. For $\sigma = 0$, cooperation satisfies none of the criteria for evolutionary success. However, in the affine case, each such criterion is fulfilled if the constant fitness advantage $-\sigma$ is higher than the cost $\mathfrak{c}$. Thus cooperation can also arise in small populations if cooperators can compensate the cost of cooperation by a constant fitness surplus.

5 Coevolution of tumor and normal cells

Tumors present an example of the evolution of defection, because cancer cells have lost their normal cooperative behavior and defect the host (Michor et al., 2004). However, experiments indicate that tumors consist of about 50% of non-cancerous cells. This fraction appears to be consistent among distinct cancer subtypes (Van Loo et al., 2010), which raises the possibility that the normal

cells are not the result of a random admixture, but constitute an attractive equilibrium resulting from interactions of tumor and normal cells.

As shown in section 3, the two-player dynamics only depends on the difference α and β, as well as σ. For a given attractive equilibrium, there exist thus many parameter combinations. In the following, we set $x^* = (1/2, 1/2)$, which is reasonably close to the experimentally observed ratio of 49% tumor cells (Van Loo et al., 2010). We observe that this choice implies $\sigma = \frac{1}{2}(\alpha + \beta)$, which reduces the number of independent parameters to two.

To explore the range of possible parameter combinations, we define the following three tumor cell strategies to be played against a normal cell type:

$$
\begin{array}{cccc}
T_1: & \alpha_1 = -1 & \beta_1 = 1 & \sigma_1 = 0 \\
T_2: & \alpha_2 = -2 & \beta_2 = 0 & \sigma_2 = -1 \\
T_3: & \alpha_3 = 0 & \beta_3 = 2 & \sigma_3 = 1
\end{array}
\tag{30}
$$

When played pairwise against normal cells all three strategies lead to a stable equilibrium at $x_N^* = 1/2$. Tumor strategy T_1 presents a mixed strategy of exploitation and attraction of normal cells, without an additional intrinsic fitness advantage. T_2 is a strategy that strongly exploits (Prisoner's Dilemma), however at a the cost of a disadvantage in terms of the constant fitness contribution. T_3 is a mixed strategy that has both a constant fitness advantage and the ability to recruit healthy cells.

5.1 Three-player games

In large tumors a huge genetic diversity is generated due to the large number of cells and a potentially increased mutation rate (Beerenwinkel et al., 2007; Bozic et al., 2010). It is thus likely that many different tumor cell types with specific strategies are present in the tumor simultaneously. Hence a strategy able to dominate many others will be successful in taking over a tumor.

Let H denote the normal (healthy) cell type and T_1 a tumor strategy. Again there is an affine payoff function for the tumor-normal interaction with the payoff matrix $\boldsymbol{M}$ and constant fitness $\mathbf{r}$. Now consider a second tumor strategy T_2. Assuming no interactions among the tumor cell types, the payoff matrix and fitness vector for the three strategies are

$$
\boldsymbol{M} = \begin{array}{c} \\ H \\ T_1 \\ T_2 \end{array}
\begin{array}{c} \begin{array}{ccc} H & T_1 & T_2 \end{array} \\ \begin{pmatrix} a & b_1 & b_2 \\ c_1 & d_1 & 0 \\ c_2 & 0 & d_2 \end{pmatrix} \end{array}, \qquad
\mathbf{r} = \begin{pmatrix} s \\ t_1 \\ t_2 \end{pmatrix}.
\tag{31}
$$

According to Theorem 1 the affine fitness function can be rewritten in terms of the game

$$
\boldsymbol{M}' = \begin{array}{c} \\ H \\ T_1 \\ T_2 \end{array}
\begin{array}{c} \begin{array}{ccc} H & T_1 & T_2 \end{array} \\ \begin{pmatrix} 0 & 0 & 0 \\ -\alpha_1 + \sigma_1 & -\beta_1 + \sigma_1 & -b_2 + \sigma_1 \\ -\alpha_2 + \sigma_2 & -b_1 + \sigma_2 & -\beta_2 + \sigma_2 \end{pmatrix} \end{array},
\tag{32}
$$

where the first row has been subtracted from all rows to obtain a representation in terms of α_i, β_i, and σ_i, $i = 1, 2$. Interestingly, the constant fitness terms lead to an effective interaction term among the tumor strategies. Moreover, the interactions, $m'_{T_1, T_2} = -b_1 + \sigma_2$ and $m'_{T_2, T_1} = -b_2 + \sigma_1$, depend on the absolute value of b_1 and b_2, i.e., on the payoff that a tumor pays to the fitness of normal cells.

We now investigate the replicator dynamics for the transformed game defined in Eq. 32 and the tumor strategies defined in Eq. 30, following Hofbauer and Sigmund (1998); Bomze (1983). One has $\alpha_i - \sigma_i = -1$, and $\beta_i - \sigma_i = 1$, $i = 1, \ldots, 3$. We also assume that $b_1 = b_2 =: b$, any difference can be subsumed into the parameters β_i. It follows that

$$
\boldsymbol{M'} = \begin{array}{c} \\ H \\ T_1 \\ T_2 \end{array} \begin{array}{c} H \qquad T_1 \qquad T_2 \end{array} \left(\begin{array}{ccc} 0 & 0 & 0 \\ 1 & -1 & -b - \sigma_1 \\ 1 & -b - \sigma_2 & -1 \end{array} \right) \tag{33}
$$

This game has the non-trivial fixed points $x^* = (1/2, 1/2, 0)^\top$, and $x^* = (1/2, 0, 1/2)^\top$. However, it depends on the parameter b whether these are stable or saddle points. As shown in Appendix A, there exists an additional fixed point in the interior of S_2 at

$$
x^* = (\omega_1, \omega_2, \omega_3)^\top / \omega \tag{34}
$$

with

$$
\begin{aligned}
\omega_1 &= 1 - (b - \sigma_1)(b - \sigma_2) \\
\omega_2 &= 1 - (b - \sigma_1) \\
\omega_3 &= 1 - (b - \sigma_2),
\end{aligned} \tag{35}
$$

and $\omega = \sum \omega_i$, if, and only if, all ω_i have the same sign, $\operatorname{sgn} \omega_1 = \operatorname{sgn} \omega_2 = \operatorname{sgn} \omega_3$ (Stadler and Schuster, 1990).

The dynamic behavior of all three player games HT_iT_j of the normal cell type with two of the tumor strategies T_1, T_2, and T_3 can be divided into the following four cases:

(i) For

$$
b < \frac{\sigma_1 + \sigma_2}{2} - \sqrt{\left(\frac{\sigma_1 + \sigma_2}{2}\right)^2 - (1 - \sigma_1 \sigma_2)} \tag{36}
$$

the normal cell type goes extinct. There exist only a stable equilibrium of the two tumor strategies. In this case the constant fitness advantages of both tumor types are so large that despite the payoff b to the normal cell type, H dies out.

(ii) In the regime

$$
\frac{\sigma_1 + \sigma_2}{2} - \sqrt{\left(\frac{\sigma_1 + \sigma_2}{2}\right)^2 - (1 - \sigma_1 \sigma_2)} < b < 1 + \min\{\sigma_1, \sigma_2\} \tag{37}
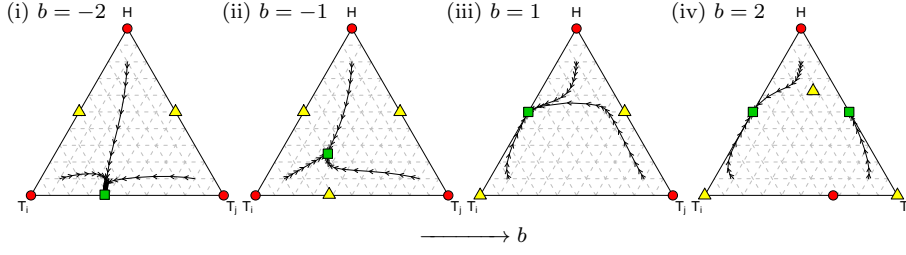$$

Fig. 2 Illustration of the dynamic regimes (i)–(iv). Specific values are for the game NT_1T_2 for different values of the parameter b. Red circles denote unstable fixed points, yellow triangles are saddle points, and green squares are stable equilibria. For case (iii), the fixed point on the edge NT_i for the tumor strategy T_i with $\sigma_i > \sigma_j$ is stable.

there exists a stable fixed point in the interior of the simplex. Hence all three cell types coexist. In this regime the constant fitness advantage of both tumor types are smaller than the fitness but not too large to have the normal cell type go extinct.

(iii) If

$$1 + \min\{\sigma_1, \sigma_2\} < b < 1 + \max\{\sigma_1, \sigma_2\} \tag{38}$$

there exists no interior fixed point. Then only the fixed point $x_H = 1/2$, $x_{T_i} = 1/2$, for $\sigma_i > \sigma_j$ is stable. That is, the tumor strategy that has the larger fitness advantage will win. Equivalently, we can write $\min\{t_1 - s, t_2 - s\} < b - 1 < \max\{t_1 - s, t_2 - s\}$. In this case, the constant fitness advantage of one tumor type is smaller than the payoff b minus 1, whereas the other tumor types' fitness advantage exceeds this value.

(iv) Lastly, for

$$b > 1 + \max\{\sigma_1, \sigma_2\} \tag{39}$$

there exists an interior saddle point and both fixed points at the edges, $x^* = (1/2, 1/2, 0)^\top$, and $x^* = (1/2, 0, 1/2)\top$ are stable. Which tumor strategy wins, depends on which of the two tumor strategies emerged first. The condition is equivalent to $b > 1 + \max\{t_1, t_2\} - s$. In this regime, the payoff to a normal cell b is larger than the constant fitness advantages to both tumor types plus one. Therefore, both tumor types attract normal cells more strongly than their constant fitness advantage.

The dynamics associated with each case are illustrated in Figure 2. These different cases are realized for each game at different parameter values of b. For $b = 2$ (Figure 3A), we have case (vi) for the game HT_1T_2, and case (iii) for games HT_1T_3, HT_2T_3. Thus for HT_1T_2, whichever of the strategies T_1 and T_2 arises first will be successful and converges to an equilibrium with H. In the other two games, however strategy T_3 wins over T_1, and T_2, respectively. We thus conclude that T_3 is most successful. The coordinates of the equilibrium interior equilibrium x^* defined in Eq. 34 are depicted in Figure 3D for the three games HT_1T_2, HT_1T_3, and HT_2T_3 as a function of the parameter b.

Because tumor strategy T_3 has the largest constant fitness advantage, $\sigma_3 > \sigma_1 > \sigma_2$, it outcompetes the other tumor strategies for most values
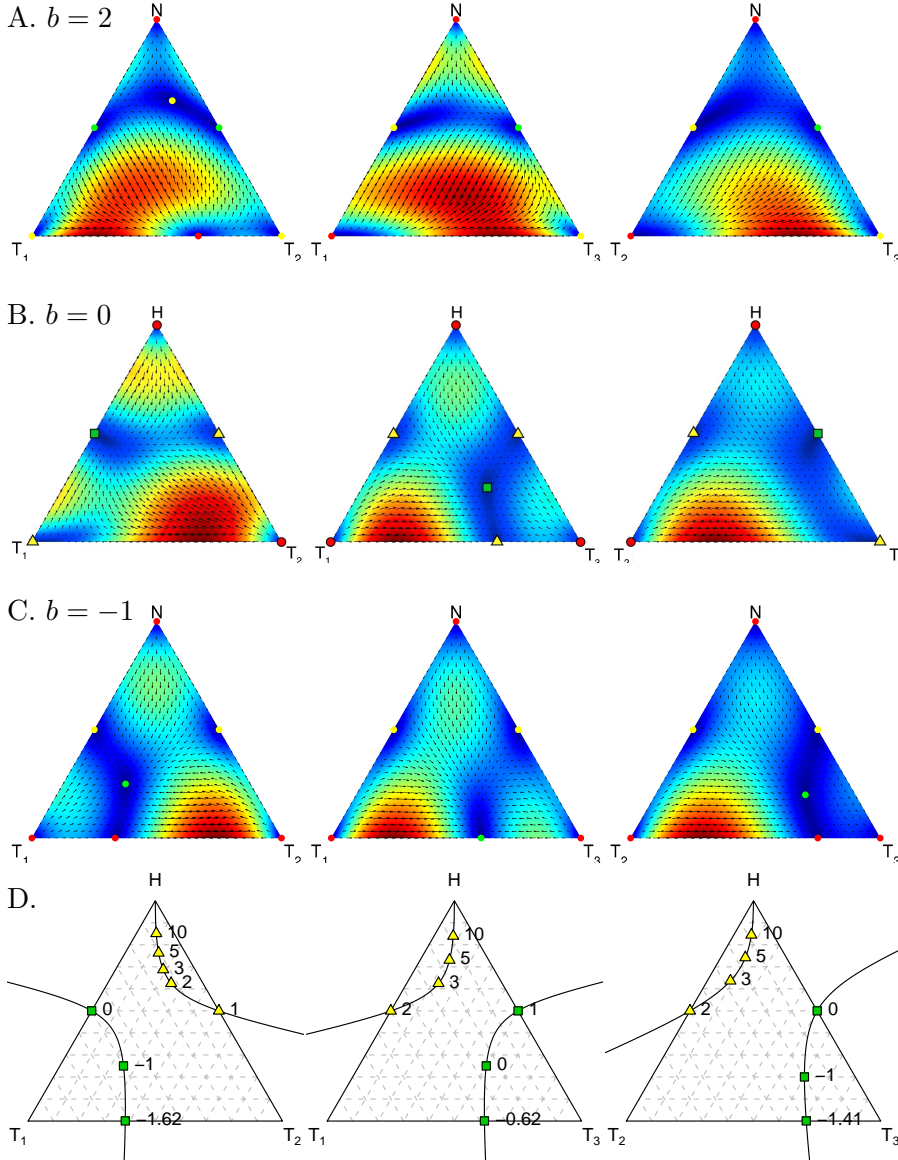
Fig. 3 A-C: Tumor strategies in the 3 player case for $b = 2, 0, -1$. Arrows denote the direction, and colors the rate of change defined by the replicator equation, Eq. 4. Points label the fixed points of the system, obtained by solving the algebraic equation defined by $\dot{x} = 0$. Red circles are repelling fixed points (two real parts of the eigenvalues λ_i, $i = 1, \ldots 3$, of the Jacobian $J(x^*)$ positive), yellow triangles: saddle points (1 real part positive), and green squares are stable fixed points with two real parts negative. D: Position and stability of the interior fixed point as a function of b for all three games. Again yellow dots denote saddle points, green circles are stable fixed points.

of b. If b is of moderate size, there exists an equilibrium with T_1 (Figure 3B). The equilibrium level lies, however, at low frequencies of T_1. There also exists a stable equilibrium with T_2 for $b < 0$ (Figure 3C). Yet the latter appears biologically unrealistic, as it would effectively repel normal cells, which contradicts the consensus of a positive interaction (Mueller and Fusenig, 2004).

Tumor strategy T_1, which both exploits and attracts normal cells, wins over T_2 for $b > 0$. This is because of the fitness disadvantage of T_2. In comparison with T_3, there is a bistable equilibrium for $b > 2$. For $0 < b < 2$, however, T_3 dominates T_2.

The affine Prisoner's Dilemma strategy T_2 performs worst of all, because it has a fitness disadvantage compared to normal cells, in contrast to the other two tumor strategies. This disadvantage is required to generate a stable equilibrium with normal cells. Due to this disadvantage, however, the strategy is easily outcompeted by T_1 and T_3.

6 Discussion

In evolutionary games with affine fitness functions, the corresponding inhomogeneous replicator equation has an equivalent homogeneous replicator equation with a transformed game. The transformations of the game, however, can cause substantial differences as compared to the original game. For $n = 2$ dimensions, the resulting changes can be fully characterized in terms of the constant fitness difference σ. The affine transformations of the payoff matrix also influence the stochastic Moran model of a finite population, and we have evaluated how different criteria for the stability of a strategy are affected.

The affine terms also alter the dynamics of the Prisoner's Dilemma game, a prototype game for studying the evolution of cooperation (Axelrod and Hamilton, 1981). In the presence of a constant fitness advantage, cooperation can arise if the fitness advantage is higher than the cost to pay for cooperation. This simple rule adds to the five rules for the evolution of cooperation that were presented recently (Nowak, 2006b). It makes precise the intuitive idea that cooperators can evolve if they compensate their disadvantage in the game by an intrinsic fitness contribution.

In mathematical and computational models of cancer, reviewed recently by Attolini and Michor (2009), evolutionary game theory provides a useful tool for analyzing the role of cell differentiation and heterogeneity in tumor initiation and progression. In the earliest studies applying evolutionary game theory to cancer, Tomlinson and Bodmer investigated the effects on tumor progression of several cell behaviors, including cytotoxicity, angiogenesis, and apoptosis (Tomlinson, 1997; Tomlinson and Bodmer, 1997). Further studies have used evolutionary game theory to model spatial dynamics (Bach et al., 2003), tumor-host interaction (Gatenby and Vincent, 2003), and the interaction of multiple tumor cell phenotypes (Bach et al., 2001), in particular those of invasive or motile cells (Mansury et al., 2006; Basanta and Deutsch, 2008; Basanta et al., 2008). In the present study, we take explicit account of the

effects of affine transformations on evolutionary games in cancer, and we use this framework to investigate interactions among cell types within the tumor population.

Tumor cells present an example where defecting strategies arise in an organism of cooperating cells. Experimental data indicates that tumor cells exist in a stable equilibrium with normal cells (Van Loo et al., 2010). We have therefore analyzed what type of tumor strategies would lead to such coexisting states by means of an inhomogeneous replicator equation. Fitness is modeled to contain both a game-theoretic and a constant term. Because most parameters of the model cannot be directly obtained by experiment, we assessed three different prototype tumor strategies leading to the same equilibrium level. To get further insight into the relative contributions of both the interactions with normal cells, and the intrinsic tumor-specific fitness, we have analyzed the dynamics of multiple tumor strategies. This approach is motivated by the finding that in large populations, new cell types arise quickly through spontaneous mutations. It is thus a requirement for a winning strategy to be able to compete with many others, although many of them are likely to exist only in very low frequencies.

The analysis of multiple tumor strategies in a three player game shows that the affine fitness function introduces correction terms that cause an effective interaction of the tumor cells. The strength of these interaction terms was given by the constant fitness advantage, and the absolute payoff of tumor to normal cells. We have then classified the dynamics of the system based on the payoff to normal cells and the constant fitness advantage. We find that the most successful tumor strategy has both a constant fitness advantage and a payoff to normal cells (relative to the payoff to itself).

The payoff to normal cells could be mediated by a mobile growth factor such as VEGF. This growth factors is secreted by tumor cells to attract blood vessels that, in turn, supply the tumor with nutrients (Mueller and Fusenig, 2004). Interestingly, the interaction through VEGF is also a target for drug interventions yet with ambivalent success (Carmeliet, 2005). Our analysis also elucidates when such an intervention would be successful: In the replicator dynamics, an equilibrium between tumor and normal cells exists only if $a - c < t - s < b - d$. A therapeutic success would occur if normal cells dominate the dynamics. This requires $a - c$ and $b - d$ to be larger than $t - s$. An VEGF inhibitor would reduce the parameter b, ideally to zero. This is however, not sufficient for the replicator dynamics to favour normal cells, because also $a - c$ must become larger than $t - s$. A successful therapy must additionally reduce c to zero such that $t - s < a$. However, this may be difficult, or even impossible, to achieve for tumor cells with a high constant fitness advantage.

In our model of tumor-normal interactions, all strategies were given. In cancer, however, new strategies are thought to arise through mutations. In the future it could thus be an interesting extension to the model to include mutations that transform one strategy into another, see for example (Fudenberg et al., 2006) for a general analysis of evolutionary game theory with mutations in finite populations. Such an extension may also be capable of assessing the

interactions with cancer stem cells, which are hypothesized to form a distinct tumor subpopulation that replenishes normal tumor cells (Wicha et al., 2006; Clarke et al., 2006).

A Fixed points of three player strategies

Rewrite matrix $\boldsymbol{M}'$ of Eq. 32 in normal form:

$$\boldsymbol{M}' = \begin{array}{c} \\ N \\ T_1 \\ T_2 \end{array} \begin{array}{ccc} N & T_1 & T_2 \\ \begin{pmatrix} 0 & \beta_1 - \sigma_1 & \beta_2 - \sigma_2 \\ -\alpha_1 + \sigma_1 & 0 & \beta_2 - b_2 - \sigma_2 + \sigma_1 \\ -\alpha_2 + \sigma_2 & \beta_1 - b_1 - \sigma_1 + \sigma_2 & 0 \end{pmatrix} \end{array} =: \begin{pmatrix} 0 & \delta & \gamma \\ \alpha & 0 & \epsilon \\ \eta & \beta & 0 \end{pmatrix}. \quad (40)$$

Now define:

$$\omega_1 = \delta\epsilon + \gamma\beta - \epsilon\beta \tag{41}$$
$$\omega_2 = \alpha\gamma + \epsilon\eta - \gamma\eta \tag{42}$$
$$\omega_3 = \eta\delta + \alpha\beta - \alpha\delta \tag{43}$$

One finds:

$$\omega_1 = (\beta_1 - \sigma_1)(\beta_2 - \sigma_2) - (b_1 - \sigma_2)(b_2 - \sigma_1) \tag{44}$$
$$\omega_2 = (\alpha_2 - \sigma_2)(b_2 - \sigma_1) - (\alpha_1 - \sigma_1)(\beta_2 - \sigma_2) \tag{45}$$
$$\omega_3 = (\alpha_1 - \sigma_1)(b_1 - \sigma_2) - (\alpha_2 - \sigma_2)(\beta_1 - \sigma_1), \tag{46}$$

It can be shown (Stadler and Schuster, 1990) that there exists a fixed point in the interior of S_2, iff all ω_i, $i = 1, \ldots, 3$ have the same sign, $\mathrm{sgn}\,\omega_i = \Sigma$ (Stadler and Schuster, 1990). Its coordinates are given by $x^* = (\omega_1, \omega_2, \omega_3)^\top/\omega$. The stability of x^* is determined by the determinant $\Delta = \alpha\beta\gamma + \delta\epsilon\eta$, that is:

$$\begin{aligned} \Delta = &(\alpha_1 - \sigma_1)(b_1 - \sigma_2)(\beta_2 - \sigma_2) + (\alpha_2 - \sigma_2)(b_2 - \sigma_1)(\beta_1 - \sigma_1) \\ &- (\beta_1 - \sigma_1)(\beta_2 - \sigma_2)(\alpha_1 - \sigma_1 + \alpha_2 - \sigma_2). \end{aligned} \tag{47}$$

The interior fixed point is stable iff both eigenvalues of the Jacobian, $\lambda_{1/2} = -\Sigma(\Delta \pm \sqrt{\Delta^2 - 4\omega_1\omega_2\omega_3})$, have negative real parts. This requires that $\mathrm{sgn}\,\Delta > 0$, and $\Sigma > 0$. Hence all ω_i need to be positive.

These conditions simplify for the tumor strategies defined in Eq. 30. These imply $\alpha_i - \sigma_i = -1$, and $\beta_i - \sigma_i = 1$, $i = 1, \ldots, 3$. With the additional assumption $b_i = b$, $i = 1, \ldots, 3$, it follows that

$$\omega_1 = 1 - (b - \sigma_1)(b - \sigma_2)$$
$$\omega_2 = 1 - (b - \sigma_1)$$
$$\omega_3 = 1 - (b - \sigma_2).$$

The determinant reads

$$\Delta = 2 - (b - \sigma_1) - (b - \sigma_2) = \omega_2 + \omega_3. \tag{48}$$

Hence the condition $\mathrm{sgn}\,\Delta = \Sigma$ is fulfilled if $\mathrm{sgn}\,\omega_1 = \mathrm{sgn}\,\omega_2 = \Sigma$. The conditions for each ω_i to be positive are:

$$\omega_1 > 0 \quad \Leftrightarrow \quad \left| b + \frac{\sigma_1 + \sigma_2}{2} \right| < \sqrt{\left(\frac{\sigma_1 + \sigma_2}{2}\right)^2 - (1 - \sigma_1\sigma_2)} \tag{49}$$
$$\omega_2 > 0 \quad \Leftrightarrow \quad b > 1 + \sigma_1 \tag{50}$$
$$\omega_3 > 0 \quad \Leftrightarrow \quad b > 1 + \sigma_2 \tag{51}$$

For the parameter values of the tumor strategies T_i considered here, $\omega_1 < 0$ if both ω_2, and ω_3 are negative. It thus follows that all three ω_i are negative, iff $b > 1 + \max\{\sigma_1, \sigma_2\}$. Then the interior fixed point x^* is unstable. For the interior fixed point to be stable, all three conditions Eq. 33–35 need to be fulfilled.

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